DETAILED ACTION

Election/Restrictions

Applicants have elected group I of the restriction. X is n, Y is C=O, and p and q are each 2, R9, R2,R3, R4 are all H or CN or an alkyl of formula I, claims 1-9, and new claims 11-20.

The examiner has expanded the group to include claim 8 formula III,

The examiner has agreed for a rejoinder of the method claims limited to the same scope if the compound claims were found to be allowable.

See restriction requirement page 5.

Priority

This application is a 371 of International Application No. PCT/IB2004/004108 filed December 9, 2004, which claims priority to GB 0328906.3 filed December 12, 2003,

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for some R8 and R3 substituents does not reasonably provide enablement for the broad scope as claimed. The language of the claims and substitutents R1 and R8 with generic groups and optionally substituted covers practically any group. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

1) The breadth of the claims: The instant claims encompass many compounds with a different substituents off of it.

R^{l} is hydrogen, optionally substituted alkyl, optionally substituted alkoxycarbonyl, optionally substituted alkylcarbonyl, aminocarbonyl, optionally substituted alkylaminocarbonyl, optionally substituted dialkylaminocarbonyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, optionally substituted heterocyclyloxy, cyano, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, formyl, optionally substituted heterocyclyl, optionally substituted alkylthio, NO or NRI3RI4;

~R^{13} and R^{14} are each independently hydrogen, $COR^{15,}$ optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclyl or R^{13} and R^{14} together with the N atom to which they are attached form a group _N=C(R16)_NR17RI8;

R^{15} is H, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryi, optionally substituted aryloxy optionally substituted heteroaryl, optionally substituted heteroaryloxy or NR19R2°;

$R^{16,}$ R^{17} and R^{18} are each independently H or lower alkyl;

R^{19} and $R^{2°}$ are independently optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl;

R^{2} and R^{3} are independently hydrogen, halogen, cyano, optionally substituted alkyl, optionally substituted alkoxy or optionally substituted aryl;

each R^{4} is independently halogen, nitro, cyano, optionally substituted C1-8 alkyl, optionally substituted C2-6 alkenyl, optionally substituted C2.6 alkynyl, optionally substituted alkoxycarbonyl, optionally substituted alkylcarbonyi, optionally substituted alkylaminocarbonyl, optionally substituted dialkylaminocarbonyl, optionally substituted C3-7 cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, optionally substituted alkylthio or R21R22N; ,,vher-e-R^{21} and R^{22} are; each independently; hydrogen, Ci-8 alkyl, C3.7 cycloalkyi, C3-6alkenyl, C3-6 alkynyl, C3-7 cycloalkyl(Cl_a)alkyl, C2-6 haloalkyl, C1-6 alkoxy(C~.6)alkyl, or Ci-6 alkoxycarbonyl or R^{21} and R^{22} together with the N atom to which they are attached form a five, six or seven-membered heterocyclic ring which may contain one or two further heteroatoms

selected from O, N or S and which may be optionally substituted by one or two Cl.6 alkyl groups;i

or 2 adjacent groups R^a together with the carbon atoms to which they are attached form a 4, 5, 6,_or 7 membered carbocyclic or heterocyclic ring which may be optionally substituted by halogen;

n is 0, 1, 2, 3 or 4;
each Ra is independently hydrogen, halogen, hydroxy, cyano, optionally substituted Cl-8 alkyl, optionally substituted C2-6 alkenyl, optionally substituted C2.6 alkynyl, optionally substituted alkoxycarbonyl, optionally substituted alkylcarbonyl, optionally substituted alkylaminocarbonyl, optionally substituted dialkylamino'carbonyl, optionally substituted C3-7 cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted

2) The nature of the invention: The invention is a chemical compound used as a pharmaceutical.

3) The state of the prior art: The state of the prior art is that the drugs and the enzymes react in a lock and key mechanism and the structure of the compound has to be specific. Even a difference of a methyl group verses a hydrogen changes the properties altogether. A good example is a theophylline verses caffeine. They differ by just a methyl group but one of them has a pharmaceutical use as a bronchodilator. There is no absolute predictability and no established correlation between the different substitutions on a core that they would all behave in the exact same way. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

Also the state of the prior art is that it involves screening in vitro and invivo to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability and no established correlation between in vitro activity and the treatment of diseases as the in vitro data is not a reliable predictor of success even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

4) The level of one of ordinary skill: The ordinary artisan is highly skilled.

5) The level of predictability in the art:
How to use:- It is noted that the pharmaceutical art is unpredictable , requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statue. The level of unpredictability is in the art is very high. The compounds which differ by a methyl group also show different properties, for e.g. theophylline and caffeine. One of them is a bronchodilator and they differ only by a methyl

group. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).

How to make :-

As stated in the preface to a recent treatise:

"Most non-chemists would probably be horrified if they wereto learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work .....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)

....." Dorwald F. A.

Side Reactions in Organic Synthesis, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

Thus it is not very easy to synthesis compounds.

6) The amount of direction provided by the inventor: The inventor provides very little direction in the instant specification. There are various groups at the R3 and R8 positions but the language used to claim these groups is very large and ha
The availability of the starting material that is needed to prepare the invention as claimed is at issue here.. As per MPEP 2164.01 (b): In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in In re Ghiron, 442 F.2d 985, 991,169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

7) The existence of working examples: The instant specification does not have any working examples with respect to the various substitutents as given above.
8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: In view of all the above factors, guidance and state of the art , it would require an undue amount of experimentation to make the invention of the claims with various substitutents , or for using them to treat the diseases ie. Pharmaceutical compositions also..

Taking the above eight factors into consideration, it is not seen where the instant specification enables the ordinary artisan to make and/or use the instantly claimed invention.

Genetech Inc Vs Nova Nordisk 42 USPQ 2d 1001.

"A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention , not for vague intimations of general ideas that may or may not be workable."

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that,

based on the evidence regarding each of the above factors, the specification, at the time the application was flied, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Conclusion

Claims 1-9 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RITA DESAI whose telephone number is (571)272-0684. The examiner can normally be reached on Maxi- flex time..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Rita J. Desai/
Primary Examiner, Art Unit 1625

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